

REMARKS

Claims 1-35 are currently pending in the application. Claims 14-34 are withdrawn. Claim 35 is cancelled without prejudice. Applicants reserve the right to pursue subject matter affected by such amendment(s) in later-filed or co-pending continuation/divisional applications.

Applicants note the provisional obviousness-type double patenting rejection of claims 1-13. Applicants respectfully reaffirm that this provisional obviousness double patenting rejection is being held in abeyance until such time that it is clear the claims of co-pending application No. 10/410322 or co-pending application No. 10/489807 will be patented before the claims of the subject application.

Claims 6 and 7 are rejected under 35 USC§112, first paragraph, as not complying with the written description requirement. Applicants respectfully traverse. The Office Action rejects the use of the language “facilitating substances” on the grounds that such substances are only defined specifically by what they do and not what they actually are. The name “facilitating substances” is based on functional properties because many substances with different structures facilitate transport across the blood-brain barrier (Prokai, 1998; Begley et al., 2000; Cornford and Cornford, 2002; Misra et al., 2003). Some examples of the facilitating substances known before the subject patent application was submitted include the following (full cites provided on Attachment A):

1. Substances causing temporary blood-brain barrier disruption (e.g. osmotic, chemical, biochemical, etc.) and nonspecific opening for both low molecular weight molecules and macromolecules include: membrane active agents like bile salts, oleic acid; the cytotoxic drugs (etoposide, melphalan), cytochalasin B; solvents (e.g. dimethyl sulfoxide, ethanol); metals (e.g. aluminium); antineoplastic agents (e.g. VP-16, cisplatin, hydroxylurea, flurouracil, etoposide (Misra et al., 2003); the lowering pH buffer (e.g. Intracrid); hypertonic solutions of mannitol, arabinose, lactamide, saline, urea, and several radiographic contrast agents (Rapoport, 1970; Brightman et al., 1973); vasoactive amine bradykinin and its synthetic agonists (e.g. labradimil, RMP-7) (Emerich et al., 2001); histamine (Abbott and Romero, 1996; Emerich et al., 2001); eukotrienes and sulfidopeptide leukotrienes (e.g. LTC₄, LTD₄, LTE₄ and LTF₄) (Chio et al., 1992); 5-lipoxygenase inhibitors (BW755C, nordihydroguaiaretic acid, and AA-861) (Baba et al., 1992).

2. Protein kinase C (PKC) activators. Stimulation of the PKC pathway is reported to increase blood-brain barrier permeability, including the transport of amino acids across the blood-brain barrier (Ermisch A et al., 1988; Lynch et al., 1990; Rubin and Staddon, 1999). Thereby any compound activating PKC potentially can act as “facilitating substance”. For example, a PKC activator phorbol myristate acetate (PMA) was demonstrated to increase of blood barrier permeability (Lynch et al., 1990; Kaya et al., 1996). The PKC activators might be one of the following: naturally occurring diacylglycerols and their synthetic analogs (Marquez and Blumberg, 2003) (e.g. alkyl analogs: 1-oleoyl-2-acetyl-sn-glycerol 1-O-decyl-2-O-decanoylglycerol, 1-O-decanoyl-2-O-decylglycerol, 1,2-O-didecylglycerol, 1-O-hexadecyl-2-O-acetylglycerol and 1-O-decyl-2-O-acetylglycerol (Heymans et al., 1987); ether-linked diglycerides: 1-O-hexadec-1'-enyl-2-octa-dec-9'-enoyl-sn-glycerol and 1-O-hexadecyl-2-octa-dec-9'-enoyl-sn-glycerol (Ford et al., 1989), phorbol esters (e.g. PMA) (Lynch et al., 1990; Kaya et al., 1996), Cholesterol sulfate (Kuroki et al., 2000)

3. There are several polymeric compounds and nanoscopic supramolecular structures or compositions including polymeric micelles, biodegradable polymer wafers, microspheres, nanoparticles (Begley et al., 2000; Kwon, 2003; Misra et al., 2003), immunoliposomes (Huwyler et al., 1996; Cornford and Cornford, 2002). They have been shown to increase nonselective permeability of blood-brain barrier.

4. Direct chemical conjugation of peptide vectors and drugs (Prokai, 1998; Begley et al., 2000; Cornford and Cornford, 2002; Drin et al., 2002).

Based on the above documented prior art concerning substances facilitating transfer across the blood brain barrier, known at the time the subject application was submitted, one skilled in the art would appreciate that the term “facilitating substances”, in view of the further exposition of this term at page 11 of the subject application, would include the foregoing substances. What is critical is that the applicants were aware that such substances existed and that they were described in the specification and claims in such a manner as to convey possession of such substances. In view of the foregoing, applicants respectfully request the reconsideration and withdrawal of this 35 USC §112, first paragraph rejection.

Claims 1-10 are rejected under 35 USC §103(a) as being obvious over Liechty et al. Applicants believe that the amendments to claim 1 above obviate this rejection. Claim 1 has been amended to replace the transitional phrase “comprising” with the transitional phrase “consisting essentially of.” The Aminosyn RF infusion referred to in Liechty includes high concentrations of many non-aromatic amino acids, specifically large

neutral amino acids.

Liechty et al. (1999) intravenously infused a mixture of amino acids, Aminosyn, in order to provide nutritional supplementation for the growth-retarded fetus. Their Method did not change the whole-blood concentration of L-tyrosine, while L-phenylalanine was increased by only $\sim 75 \mu\text{M}$. Aminosyn in combination with glycyl-L-tyrosine increased both L-phenylalanine and L-tyrosine by $\sim 30 \mu\text{M}$. Aminosyn contains a broad range of L-form of amino acids which potentially can attenuate the neuroprotective effects of aromatic amino acids. For example, large neutral amino acids decrease transport of aromatic amino acids across the blood-brain barrier (Fernstrom and Wurtman, 1972); in addition, Aminosyn contains high concentration of glycine and alanine, which were demonstrated to eliminate inhibitory effect of L-phenylalanine on the NMDA receptors (Glushakov et al., 2002). In contrast to Aminosyn, claim 1 describes compositions that consist of L- and/or D-forms of aromatic amino acids and/or their derivatives, without the presence of interfering substances, in view of the transitional phrase “consisting essentially of”.

Accordingly, the inclusion of high concentrations of a broad variety of amino acids materially changes the nature of the composition. Thus, the Liechty et al. composition is distinguished from the compositions claimed in amended claim 1. As claims 2-11 and 13 are construed to contained all the limitations of the independent base claim 1, the Liechty et al. reference is distinguished from such dependent claims as well. Therefore, Applicants respectfully request the reconsideration and withdrawal of this 35 USC §103(a) rejection.

Claims 1, 2, 4, 5, 8-10 and 35 are rejected under 35 USC §102(b) as being anticipated by Liechty et al. Applicants assert that the amendments to claim 1 obviate this rejection and incorporate the remarks made in rebuttal of the 103 obviousness rejection above based on the same reference. The Aminosyn RF composition taught by Liechty et al. does not teach a composition consisting essentially of an aromatic amino acid. The Aminosyn RF composition contains high concentrations of non-aromatic

amino acids which change the nature of the composition from that of a composition consisting essentially of an aromatic amino acid. The presence of high concentrations of large neutral amino acids competes for blood-brain barrier transporters, and therefore interferes with the proper administration and desired effect of the composition as claimed in amended claim 1. Furthermore, nowhere does Leichty et al. teach that it would be desirable to remove certain amino acid from the aminosyn composition, and there is no other cited motivation to do so to achieve a composition suitable for accurate administration of aromatic amino acids. Dependent claims 2, 4, 5, and 8-13 are construed to contain all the limitations of the base claim 1. Thus, the amendments to claim 1 obviate this rejection as it applies to claims depending therefrom. Applicants respectfully request the reconsideration and withdrawal of this 35 USC §102(b) rejection.

Contrary to the statement at page 4 of the last office action, a close examination of the Leichty reference shows that Leichty et al. does not teach administration of an independent infusion of Glycyl-L-tyrosine. Leichty et al. teaches Aminosyn alone or Aminosyn plus glycyl-L-tyrosine. Thus, it cannot be legitimately said that Leichty et al. teaches administration of an individual L-tyrosine. Furthermore, the use of Glycyl-L-tyrosine may not be considered as a “facilitating compound” or “carrier through blood-brain barrier”. (Himmelseher et al., 1996) demonstrated that glycyl-L-tyrosine does not cross blood-brain barrier itself and does not facilitate transport of aromatic amino acids.

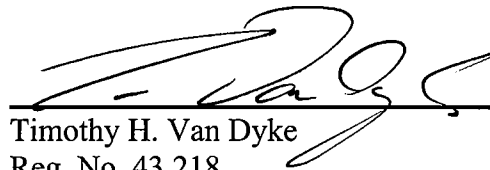
Claims 1 and 8-13 are rejected under 35 USC §102(b) as being anticipated by the Merck Index. Applicants traverse. Independent claim 1 recites a pharmaceutically accepted carrier as one of the elements of the claimed composition. The Merck Index (1996) references the use of L-tyrosine (Giancotti et al., 1980; Kierdaszuk et al., 1995), L-tryptophan (Burstein et al., 1973; Pokalsky et al., 1995) and L-Phenylalanine (Patent No. 3,492,131) as components of proteins or peptides. In contrast, the subject patent application describes an article of manufacture containing a composition intended for administration that comprises free aromatic amino acids and/or their derivatives. Applicants urge that the cited Merck Index pages do not teach the combination of an aromatic amino acid with a pharmaceutically acceptable carrier as necessary to satisfy the

requirements for anticipation. Claims 8-13 are construed to contain the limitation of claim 1. Applicants respectfully request the reconsideration and withdrawal of this 35 USC §102(b) rejection.

Lastly, claims 9, 11, and 13 have been amended to address the rejection under 35 USC, 112, second paragraph. Reconsideration is requested.

All grounds for rejection or objection having been addressed and overcome herein, it is respectfully urged that this application is in condition for allowance. Applicants request that the Examiner call the undersigned if clarification is needed on any aspect of this Reply, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Timothy H. Van Dyke', is written over a solid horizontal line.

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